THE ACTION OF TETRAHYDROPAPAVEROLINE HYDROCHLORIDE

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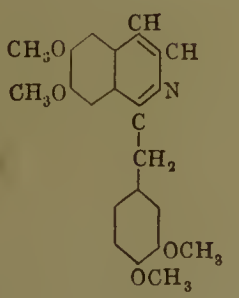
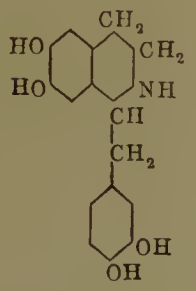
Tetrahydropapaveroline hydrochloride is a new alkaloid which was made recently by Pyman [1] during his study of the reduction products of papaverine. It presents some features of interest owing to its well-marked physiological action. The effects it produces on the normal animal are such as hold out the hope of its value as a therapeutic agent and on that account an investigation of its physiological action seemed desirable.

Its relationship to papaverine is shown in the following structural formulæ:



Papaverine



Tetrahydropapaveroline

Details of its chemical properties and relationships will be found in Pyman's paper. It may be mentioned that its hydrochloride is a white crystalline solid slightly soluble in water or saline solution. It is readily oxidised, and an alkaline solution in contact with air slowly assumes a fine purple colour and ultimately deposits a purple black amorphous precipitate. Fehling's solution and ammoniacal silver nitrate solutions are readily reduced by it.

The intact animal. On the intact animal very few effects are observable because the action of the alkaloid is not of such a kind as produces grave disturbances of the normal processes. It is moreover

not a very toxic agent. This is probably dependant on the ease with which it is oxidised. 25 mgms. of tetrahydropapaveroline hydrochloride were given to a cat hypodermically and no definite effects were observed during the next half hour beyond a slight increase in the pulse rate (before the administration the heart rate was 170 per min., after 180 per min.). This small increase might very easily have been due to other factors. At the end of the half hour 50 mgms. more were given in a capsule by mouth and the only definite alteration in the cat's condition was a further increase of the rate of heart-beat up to 228 per min., about 50 mins. after the second dose. Four guinea-pigs survived doses of 50, 50, 33 and 17 mgms. subcutaneously, and they exhibited no untoward symptoms. The heart-beat of the guinea-pig is so fast originally—usually over 300 per min.—that variations of this are not accurately distinguishable by the ordinary method of palpation.

10 mgms. were given to a rabbit intravenously and the only two effects noticed were (1) a greatly increased rate of heart-beat and (2) a quicker rate of respiration. 20 mgms. were given intravenously to the same rabbit on the following day and the same symptoms were noticed. Before the administration of the alkaloid the heart rate was 240 and the respiration 160 per min.; just after the injection the heart rate had risen to an uncountable rate (about 390) per minute and the respiration was 184. In the course of the next hour the rabbit recovered completely and the heart and respiration slowly returned to normal. At the end of the first half hour after the injection the heart was still a long way above 300 (about 384). It is thus obvious that the new alkaloid is not a very poisonous substance, and as will be seen later the doses which were given to the animals mentioned above are all capable of producing profound effects. The effects however are of a kind which are not capable of being observed in the intact animal.

A number of experiments were performed upon anæsthetised cats and rabbits. The animals were anæsthetised with chloroform, ether, ether and paraldehyde or urethane. The different anæsthetics made very little difference to the results. A number of experiments were also performed upon pithed cats. This procedure enables one to dispense with the anæsthetic which is a point of importance in studying the plain muscle of the bronchioles as was pointed out by Brodie and Dixon[2].

The vascular system. The effect of the intravenous administration of 3—10 mgms. of tetrahydropapaveroline hydrochloride to an

anæsthetised cat of 2 or 3 kilos. weight is to cause a sudden fall of blood-pressure accompanied by a greatly increased ratc of heart-beat. The blood-pressure recovers fairly rapidly after the small dosc but the heart remains very rapid for a long time (Fig. 1). Repetition of the dose gives similar results but the fall of blood-pressure is never as great as after the first dose (see Fig. 2). Very similar effects are seen when a rabbit is the experimental animal. The fall of blood-pressure is not as a rule very great. A fall of 70 mm. Hg with a dose of 3 mgms. as is shown in Fig. 1 is exceptionally large.

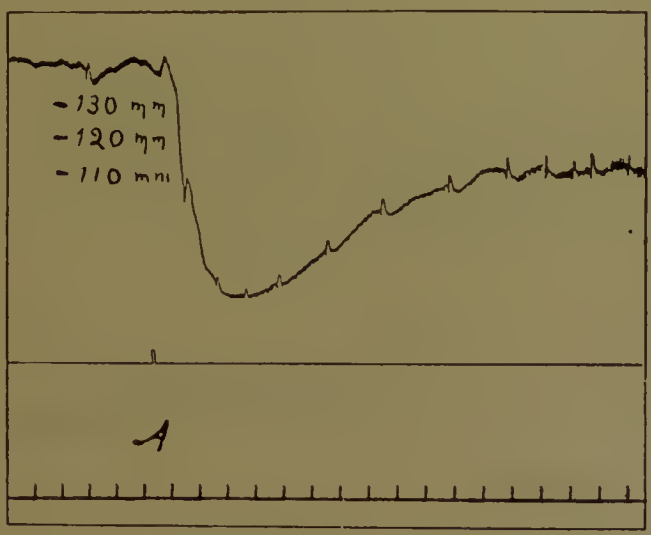


Fig. 1. Cat, ether. Blood-pressure, base liue and signal, time in 10″. The figures indicate blood-pressure levels in millimetres of mercury. Effect of injecting 3 mgrs. of tetrahydropapaveroline hydrochloride intravenously.

This fall of blood-pressure is due to a relaxation of the plain muscle of the arterioles. The flushing of thc viscera is very obvious on inspection and an increase in viscus volume demonstrated with great easc in oncometric expcrimcnts. Fig. 2 shows the effect of 8 mgms. of tetrahydropapaveroline hydrochloride on intestinal volume and blood-pressurc. Here the fall of blood-pressure is not well marked because the drug has been administered to the same animal on two occasions previously, the increase of the intestinal volume is, however, well shown. Fig. 3 shows the same result but the more usual fall of blood-pressurc as well. Similar results are seen in the experiments on kidncy volume. Accompanying the fall of blood-pressure there is a very grcat increase in cardiac activity. The rate of the heart-beat is enormously increased, particularly if the heart has been beating

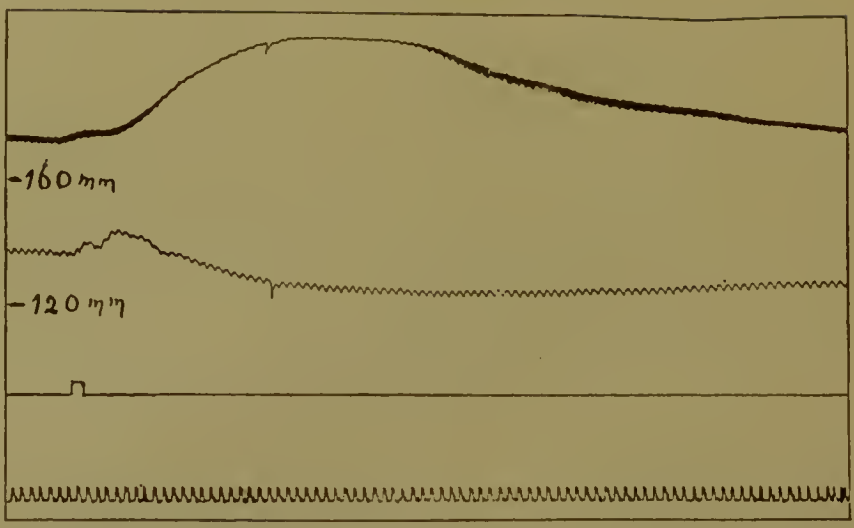


Fig. 2. Cat, ether. Intestinal volume, blood-pressure, base line and signal, time in 2″. Effect of 8 mgrs. tetrahydropapaveroline hydrochloride.

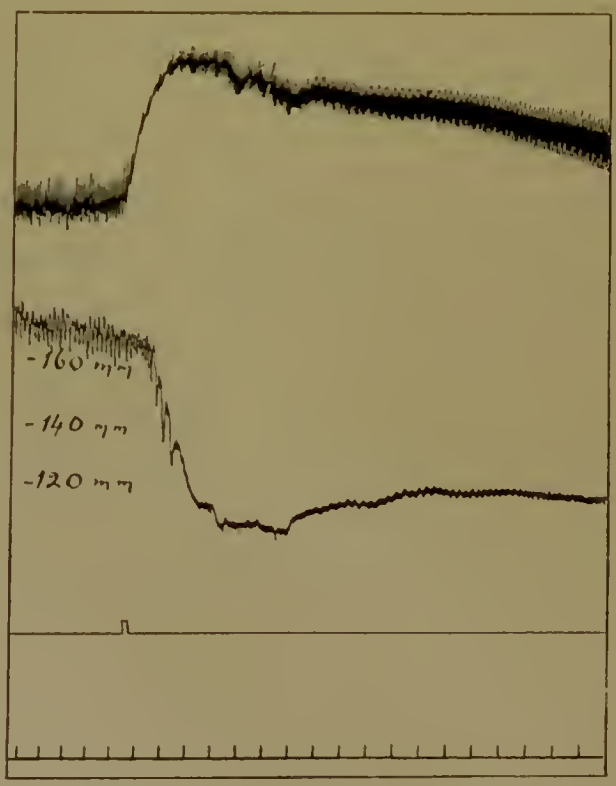


Fig. 3. Cat, ether. Intestinal volume, blood-pressure, base line and signal, time in 10″. Effect of 4 mgrs. tetrahydropapaveroline hydrochloride.

somewhat slowly before administration of the drug. In addition the force of the heart-beat is considerably augmented. These two factors are well illustrated in Figures 4 and 5. Fig. 4 shows the effect of 1 mgm. of the alkaloid injected into the perfusion cannula when an isolated cat's heart was perfused with warm oxygenated Ringer solution according to the Locke-Langendorff [3] method. It is noteworthy that the increase in size of the heart-beat is due to an increase in the completeness of systole. Fig. 5 is a cardiometer record of a cat's heart

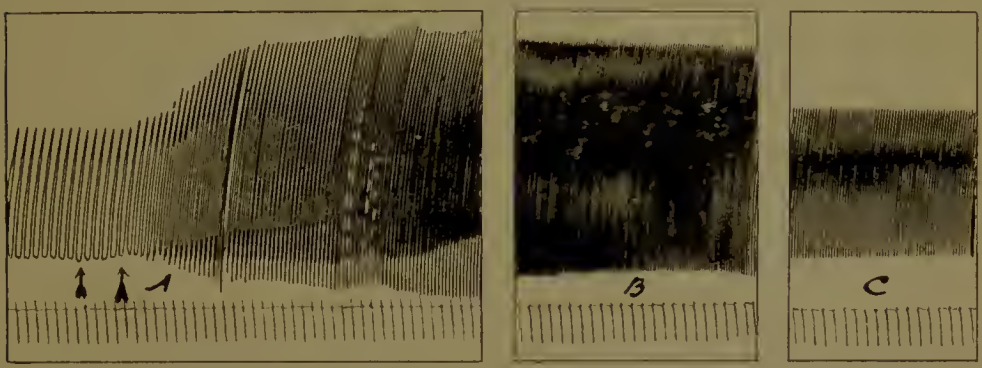


Fig. 4. Isolated heart of cat, perfused. Record from tip of left ventricle, suspension method, time in seconds. A, normal and first effect of 1 mgr. tetrahydropapaveroline hydrochloride injected into perfusion cannula. B, 1 min. after end of A; C, 3 mins. after end of B.

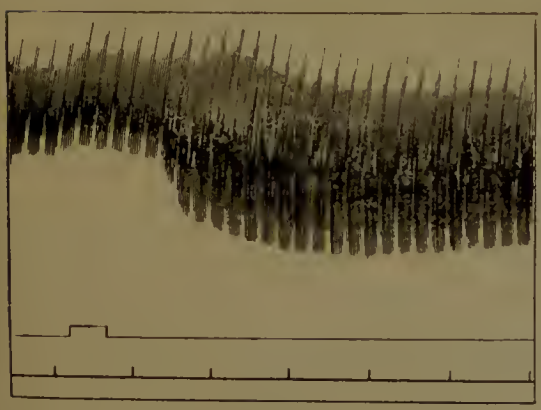


Fig. 5.

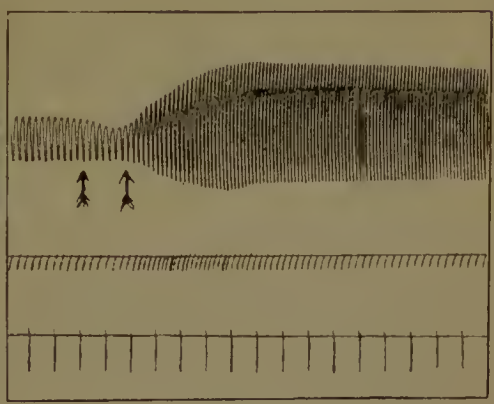


Fig. 6.

Fig. 5. Cat, pithed. Cardiometer record by bellows recorder, signal, time in 10″. Effect of 8 mgrs. tetrahydropapaveroline hydrochloride.

Fig. 6. Isolated heart of rabbit perfused after the Locke-Langendorff method. Record from tip of left ventricle, drop record of coronary outflow, time in seconds. Effect of ·5 mgr. tetrahydropapaveroline hydrochloride.

in situ. In this tracing before administration of the alkaloid the rate of heart-beat was 36 beats in 10″. The average volume per beat $= 16v$, where v is a constant depending on the size and shape of the Brodie bellows recorder. Hence the output in $10'' = 576v$.

After the administration of the drug the rate had risen to 44 beats in 10″ and the output per beat to $30v$; so that the output during the

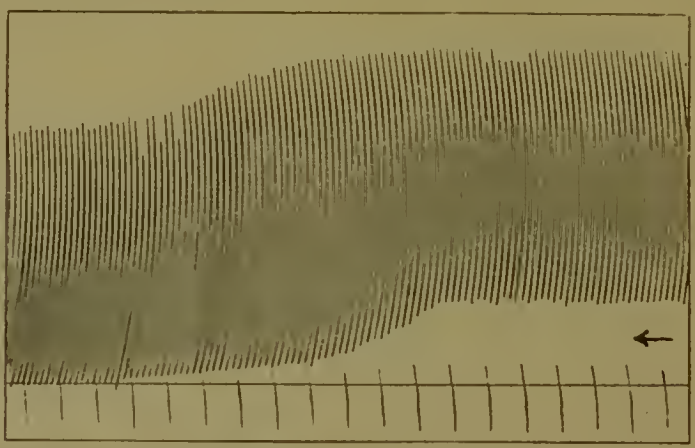


Fig. 7. Isolated heart of toad, perfused in Locke-Williams apparatus. Volume of ventricular output by Dixon frog-intestine recorder. Time in 10″. Effect of 1 in 10,000 solution of tetrahydropapaveroline hydrochloride in Ringer.

effect of the drug $= 1320v$ in 10″. It is thus evident that the output from the heart is increased by a little less than 2½ times under the influence of tetrahydropapaveroline hydrochloride and this is not an exceptional example, other records showing similar results. Fig. 7 shows the same effect on the isolated heart of the toad perfused in the Locke-Williams[1] apparatus with the Dixon frog-intestine volume recorder[4]. This large increase in cardiac output shows how a marked dilatation of the intestinal vessels can occur without a great fall of blood-pressure (see Fig. 2). The circulation time under the influence of the alkaloid must be considerably shortened. Some experiments were performed with a view to determining the effect of this alkaloid on the coronary circulation, and the results showed that the coronary circulation is practically unaffected. Fig. 6 is a record of the effect of 0·5 mgm. of the alkaloid on a rabbit's heart, with a simultaneous tracing of the coronary outflow. The Ringer solution running away from the heart

[1] This apparatus was shown at the meeting of the Physiological Society, Feb. 27, 1909, by Locke.

in numerous small drops was collected by a funnel and allowed to flow in large drops on to a drop recorder. It will be observed that, except for the slight transient increase just after the injection of the solution of the alkaloid into the perfusion cannula, the coronary flow is unaltered. The increased cardiac activity might have been expected to induce a more rapid coronary outflow. This does not seem to be the case and it is possible that a slight constriction of the coronary vessels occurs but this is rendered improbable from the fact that the plain muscle of the arterioles in the rest of the body is relaxed and, as will be seen later, plain muscle elsewhere is similarly affected. This combination of effects directly increased cardiac activity and a relaxation of the plain muscles of the arterioles is, so far as I am aware, a unique effect in response to the administration of a single drug.

Respiration. The respiration rate is considerably augmented under the influence of tetrahydropapaveroline hydrochloride but there does not seem to be much alteration in the force of the respiratory movements. Fig. 8 shows the result of the administration of 8 mgms. of the alkaloid intravenously to a cat under paraldehyde and ether anæsthesia, where the blood-pressure and respiratory movements are

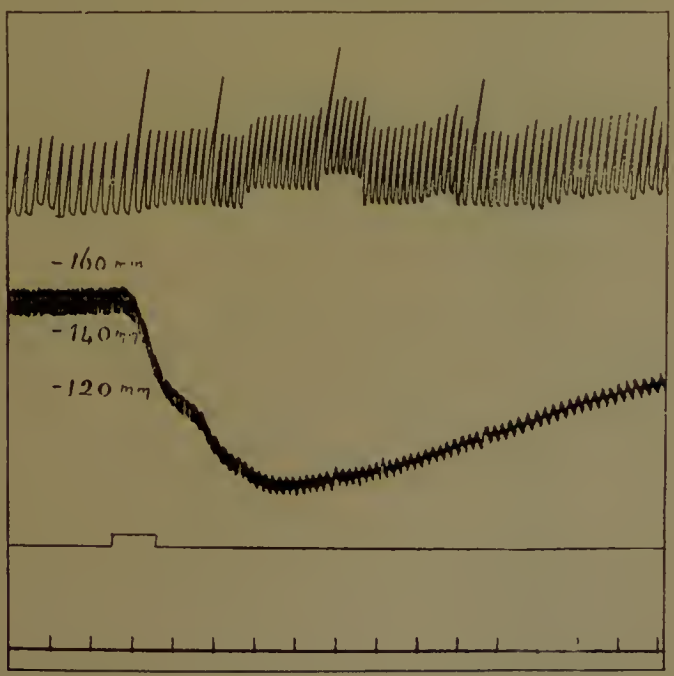


Fig. 8. Cat, paraldehyde and ether. Respiratory movements, blood-pressure, base line and signal, time in 10″. Effect of 8 mgrs. of tetrahydropapaveroline hydrochloride.

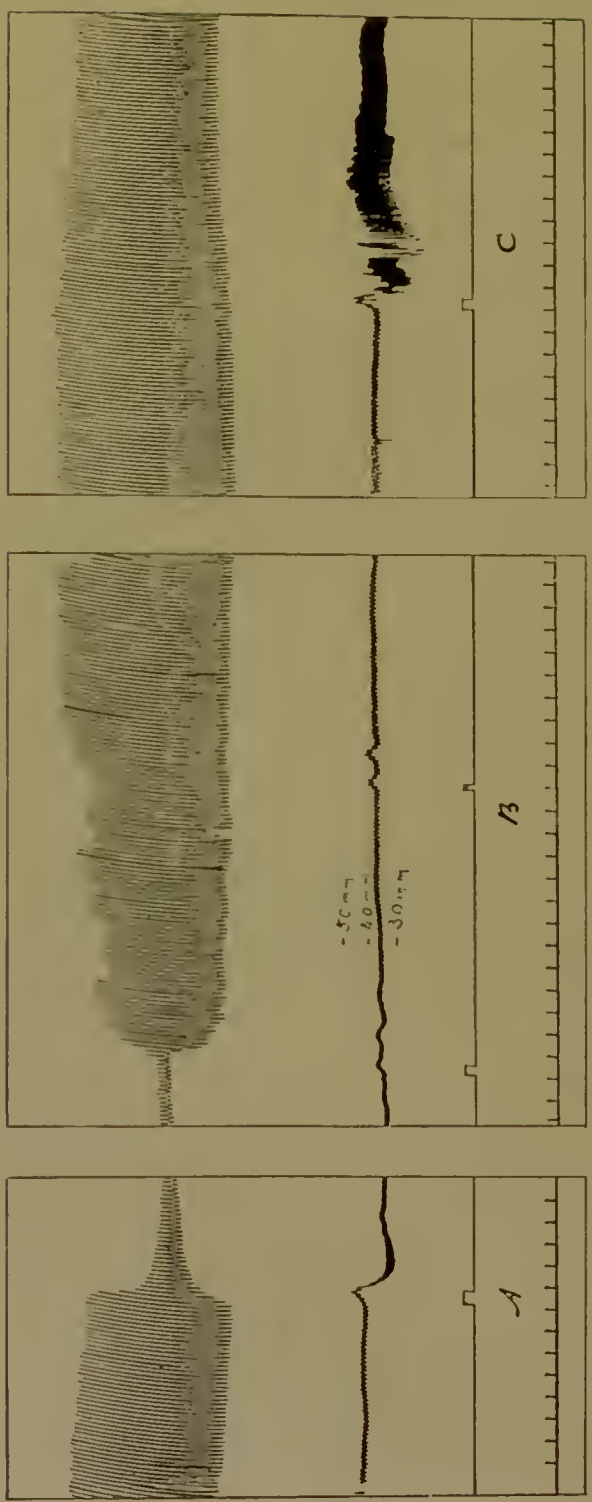


Fig. 9. Cat, pithed. Artificial respiration, volume change of one lobe of lung, blood-pressure, base line and signal, time in 10". A, normal and effect of 1 mgr. pilocarpine. B, two successive doses of 2 mgrs. tetrahydropapaveroline hydrochloride. C, 2 mins. later, 10 mgrs. of pilocarpine.

recorded simultaneously. How far the variation in the rate of the respiratory movements is secondary to the fall of blood-pressure was not investigated. The latter probably accounts for a considerable part of the increased rate of respiration. The most interesting feature of the action of tetrahydropapaveroline hydrochloride on the respiration is its effect on the plain muscle of the bronchioles. These are readily and completely relaxed by the alkaloid, and when full doses 10—20 mgms. of the alkaloid have been given intravenously it is impossible to produce spasmodic constriction of this musculature. After some rather unsuccessful attempts had been made to elucidate the point, the technique described by Brodie and Dixon [2] when studying the innervation of the bronchioles was adopted with successful results. It is necessary to open the thorax in order to enclose a lobe of lung in the plethysmograph. It is also necessary, as Brodie and Dixon point out, to use pithed animals and dispense with a volatile anæsthetic.

In all the animals used for this part of the investigation it was found that there was (by the time the operative procedure had been completed) very little and usually no tonus in the bronchiolar muscle. It became necessary therefore to induce a tonic state and see if the alkaloid would abolish it. For this purpose either (1) the vagus was stimulated or (2) pilocarpine was administered. In either case after 10—20 mgms. of tetrahydropapaveroline hydrochloride had been administered the bronchiolar muscle rapidly relaxed and vagus stimulation was then no longer capable of inducing a constriction of the bronchioles while a large dose of pilocarpine (10 mgms.) produced only a very slight constriction.

Fig. 9 is a typical example. (A) shows normal variation in ventilation of lung and the results of the administration of 1 mgm. of pilocarpine: (B) the effect of two successive doses of 2 mgms. of tetrahydropapaveroline hydrochloride: (C) the slight effect of 10 mgms. pilocarpine given subsequently. In one case where a tonic contracture persisted after stimulation of the vagus, the constriction was promptly abolished by the new alkaloid.

The uterus. A very profound effect is exerted by the alkaloid on the plain muscle of the uterus. Complete relaxation of the musculature is induced by very small doses and the effect lasts for a very long time. Whether the movements of the uterus are studied in the isolated organ or *in situ* the results are the same. Fig. 10 shows the effect of 1 mgm. of the alkaloid added to a 250 c.c. bath of warm oxygenated Ringer's solution in which a rabbit's uterus was suspended.

Very mueh smaller quantities will produce quite good relaxations, partieularly if the cat's uterus is the test object. A well-marked effect is obtained with a dilution of 1 in 2,500,000.

Fig. 11 shows the effeet on the blood-pressure and the movements of the cat's uterus studied *in situ* by the thread and pulley method. It will be seen that the result is the same as that in the isolated organ, viz. a prolonged and well-marked relaxation.

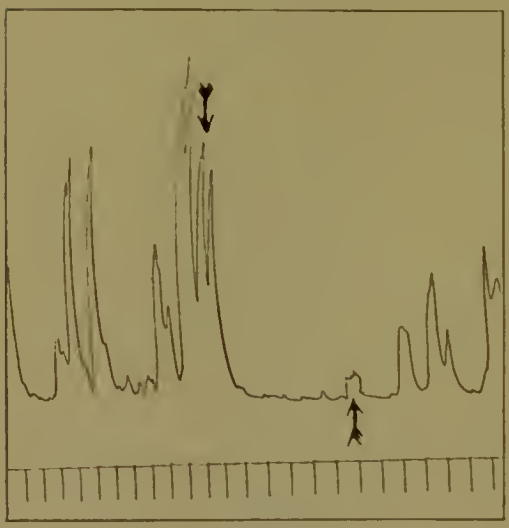


Fig. 10.

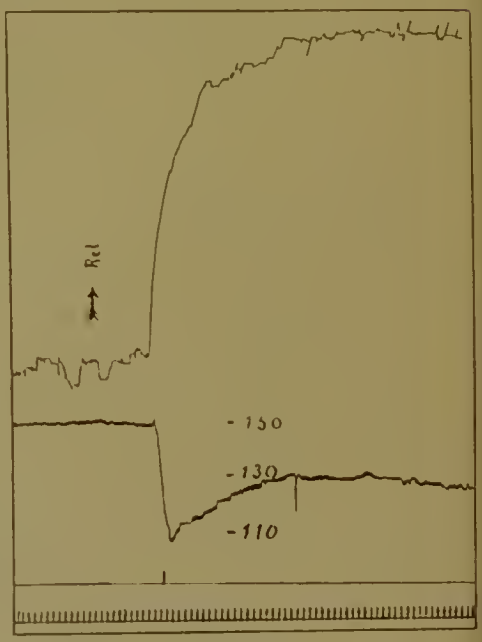


Fig. 11.

Fig. 10. Isolated rabbit's uterus in bath of 250 c.c. warm oxygenated Ringer solution. Suspension method; time in 30″. At ↓ 1 mgr. of tetrahydropapaveroline hydrochloride was added to the Ringer bath, at ↑ a change was made to fresh warm oxygenated Ringer solution.

Fig. 11. Cat in bath of saline, paraldehyde and ether anæsthesia. Uterine movements by thread and pulley method, blood-pressure, base line and signal, time in 10″. Effect of 3 mgrs. tetrahydropapaveroline hydrochloride intravenously.

The plain muscle of the intestine is also affected but to a much smaller extent. It is seen best in the isolated organ, but it also occurs in the body although the effect is not so well marked and not so persistent as the other effects recorded above. Moreover, larger doses are required to give good effects. Fig. 12 shows the effect of adding 1 mgm. of the alkaloid to a 250 c.c. Ringer bath in which a short length of rabbit's intestine was suspended. The inhibition is quite obvious but larger doses than this do not seem to produce any greater

effect. In the body the effect is not so great, and in one instance an increased vigour of intestinal peristalsis was observed. This is probably dependent on the increased blood supply to the plain muscle which occurs on administration of the drug. Fig. 13 shows the inhibition of peristalsis in the intestine of a cat.

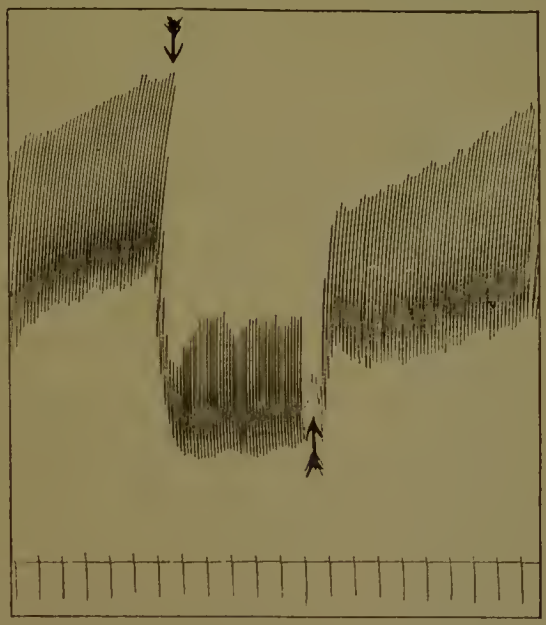


Fig. 12. Isolated rabbit's jejunum in 250 c.c. Ringer bath. Suspension method, time in 30″. At ↓ 1 mgr. tetrahydropapaveroline hydrochloride, ↑ fresh Ringer solution.

These several effects of the alkaloid on the plain muscle of the body are the result of a direct action on the muscle; because they bear no relation to innervation. Tetrahydropapaveroline hydrochloride relaxes the pregnant and non-pregnant uterus of cat or rabbit with equal facility and also the retractor penis of the dog. The bladder muscle is resistant to its effects, and does not respond like the rest of the plain musculature of the body.

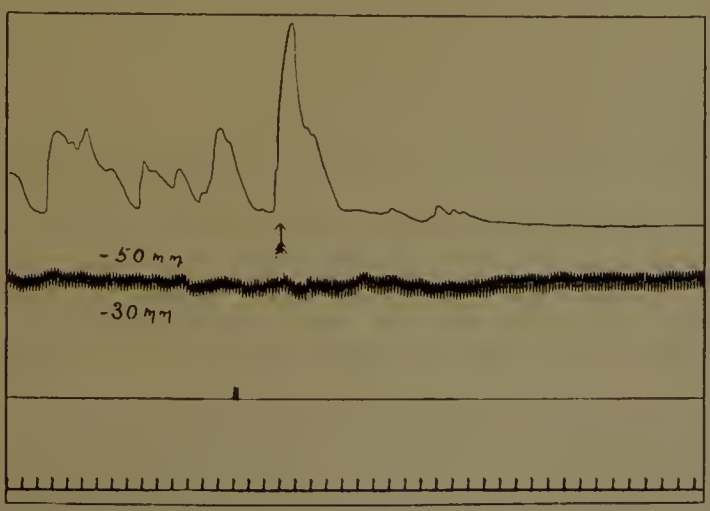


Fig. 13. Pithed cat. Intestinal movements, balloon and tambour record. Blood-pressure, base line and signal, time in 10″. Effect of 12 mgrs. of tetrahydropapaveroline hydrochloride.

On the urine flow no variation was observed other than a transient diminution probably secondary to the fall of blood-pressure.

The ease with which the alkaloid is oxidised seemed to make it probable that it is destroyed in the body. Experiments to determine its excretion or destruction were accordingly not undertaken.

Skeletal muscle appears to be unaffected by the alkaloid. No difference in response either in the irritability of a nerve-muscle preparation or the form of its contraction could be demonstrated as a result of soaking in Ringer's solution containing tetrahydropapaveroline hydrochloride to the extent of 1 part in 1000.

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